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Title: DOE/NCI Pilot 2: Molecular Determinants of Cancer

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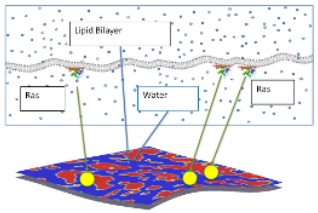
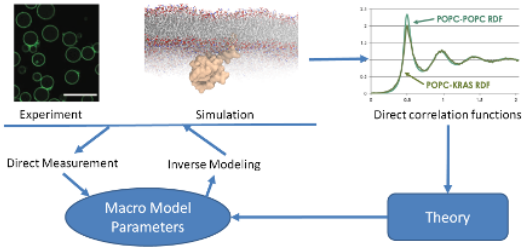
DOE/NCI Pilot 2: Molecular Determinants of Cancer

Aim 1: Spatial hierarchical multi-scale modeling

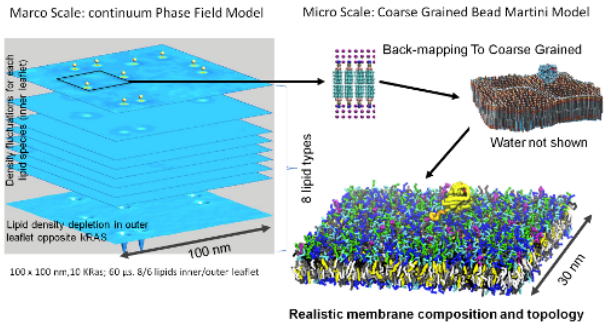
Coupled continuum and particle simulations



Macro-scale model is informed by experiment and simulation

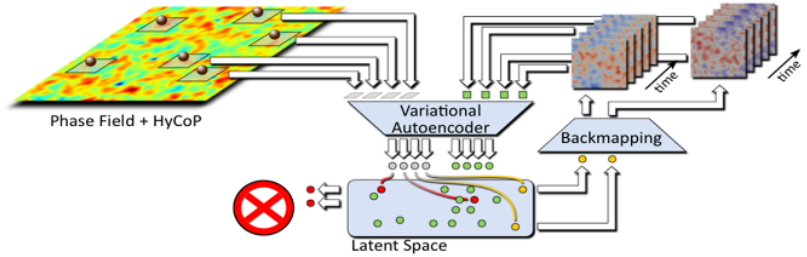


Macro to micro scale coupling



DOE	NCI
Novel multi-scale modeling framework allows investigation of continuum phenomenon informed by atomistic behavior.	Significantly enhance ability to perform predictive simulations on biologically relevant time and length scales

Aim 2: Machine-learning enabled dynamic validation approach to high-fidelity simulation



Steering multi-scale simulations by adaptively sampling data-driven latent spaces:

(1) Train latent space representing space of relevant lipid configurations.

(2) Dynamically sample configuration space to understand RAS-membrane interactions at macro time-scales with micro precision

DOE	NCI
Powerful ability to steer multiple large-scale simulations on next-generation computing, defining requirements for exascale	Combined experimental and simulation campaign of exploration leads to potential therapeutics for Ras-related cancers

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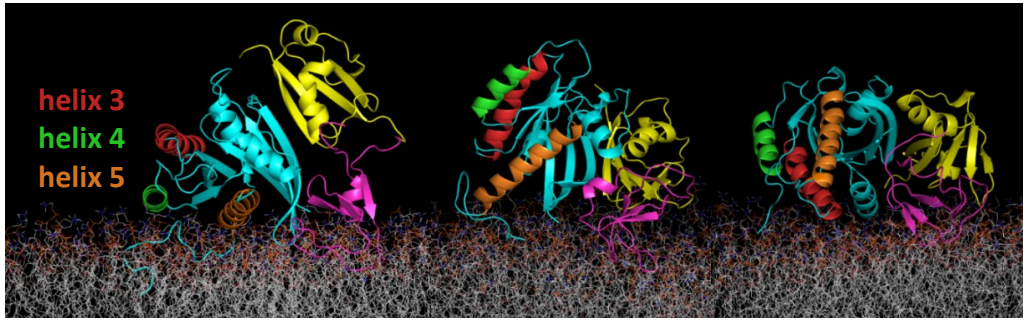
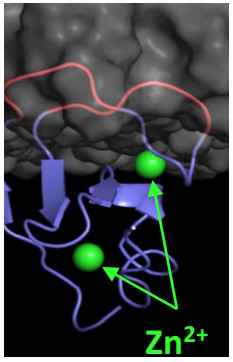
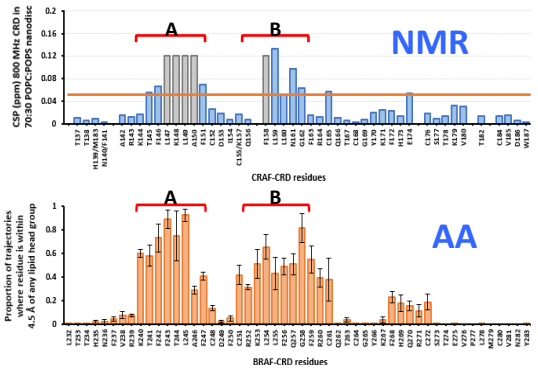


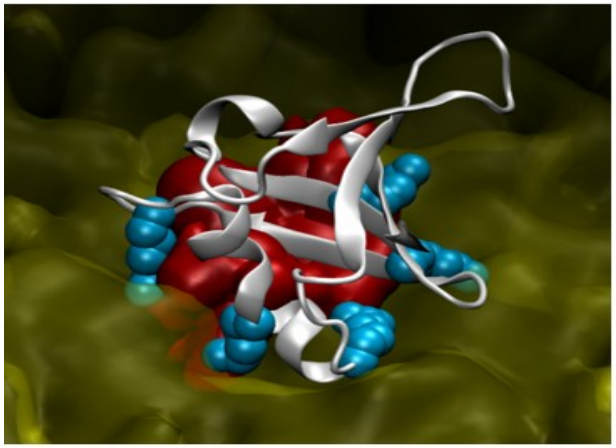
Resulting orientations: **Exposed** **Membrane-adjacent/GH5** **Membrane-adjacent/GH3**

Membrane anchoring of RAF-CRD provides a basis for exploring models of membrane-associated KRAS/RAF-RBD/RAF-CRD ternary complex

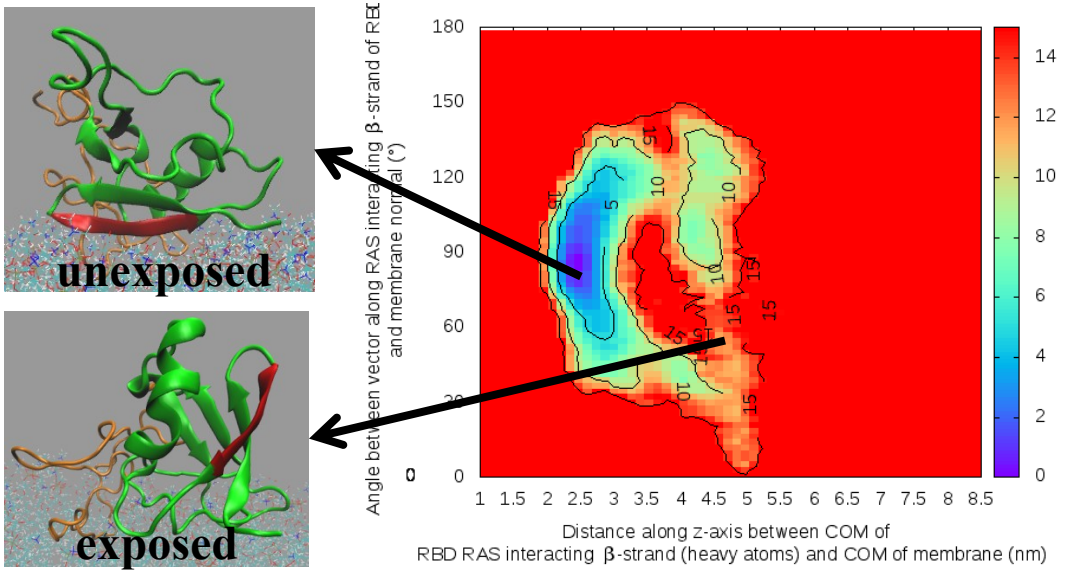




(Left) Membrane anchoring of the CRAF CRD involves two hydrophobic loops. (Right) Lipid-protein contact profiles of CRD. Larger values indicate stronger membrane association.



Weak binding of the RBD to a lipid membrane. Close contacts occur via the basic residues such as Lys and Arg (blue) of the RBD and PS lipids of the membrane. The binding of RBD is very weak due to the presence of a water layer (red) in between the RBD and membrane.



Free energy map showing the exposed and unexposed conformations adopted by the RBD, w.r.t. RAS. When the RBD is connected to the CRD, the RBD is able to explore more of the conformational space that could also lead to biologically important events.

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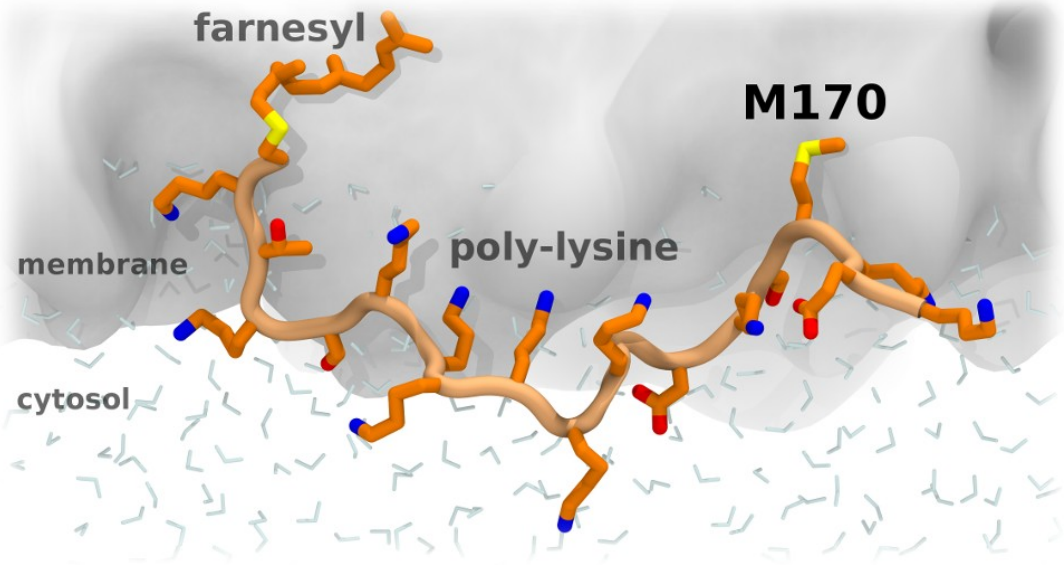
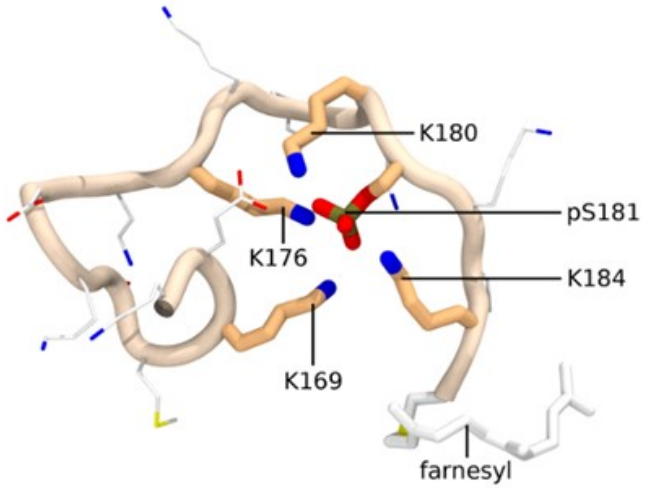
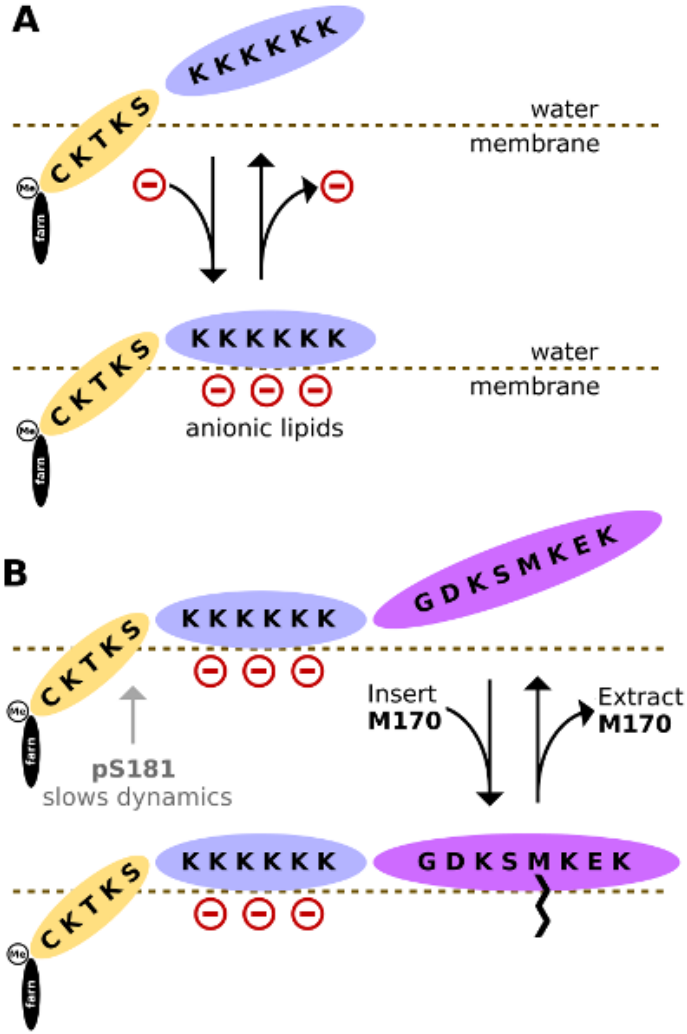


Methionine 170 is a reversible membrane anchor



Regulatory phosphorylation slows the dynamics of this anchor



Proposed model by which lipids influence Ras' membrane tether

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